REMARKS

In accordance with the present invention, it has been discovered that CREB binding protein (CBP) cooperates with upstream activators involved in the activation of transcription by signal dependent transcription factors. For example, cyclic AMP regulates the transcription of many genes (e.g., PEPCK, the rate limiting enzyme in gluconeogenesis) through protein kinase A mediated phosphorylation (at Ser133) of transcription factor CREB. Phosphorylated Ser133 CREB coordinates with a single residue of CBP, Arg600, to form a CREB:CBP complex.

It has further been discovered that the recruitment of CBP to certain inducible promoters is involved in transmitting inductive signals to the RNA polymerase II complex. Accordingly, assays employing CBP and fragments thereof have been developed for the identification of compounds which disrupt the ability of signal dependent transcription factors to activate transcription. Such compounds have utility in inhibiting gluconeogenesis, which is exhibited in diseases such as non-insulin dependent diabetes mellitus.

By the present communication, claims 1, 3, 4, 6, 7, and 8 are amended to define Applicants' invention with greater particularity. These amendments do not add any new matter as they are fully supported throughout the specification and claims as originally filed. In view of these amendments, claim 5 has been cancelled without prejudice.

After amending the claims as set forth above, claims 1-4 and 6-10 are now pending in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, beginning on page 2 of this paper under "Listing of Claims" with an appropriate defined status identifier.

I. Objections

A. Sequence Listing

The Sequence Listing has been objected to on the grounds that SEQ ID NO:2 is allegedly not the protein sequence of CREB binding protein (CBP) encoded by SEQ ID NO:1 (Office Action, page 3).

To obviate this objection, Applicants hereby request that the paper copy and the electronic copy of the Sequence Listing from parent U.S. Patent Application Serial Number 08/961,739 (filed on October 31, 1997), as submitted on July 15, 1999, be transferred to the present application.

B. Claims 7 and 8

The objection to claims 7 and 8 as allegedly being in improper dependent form (Office Action, page 4) has been rendered moot by the amendments to the claims submitted herewith. Claim 7 has been rewritten in independent form and claim 8 has been amended to depend from claim 7.

II. 35 U.S.C. § 101

The rejection of claims 7 and 8 under 35 U.S.C. § 101 as allegedly lacking utility is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that claims 7 and 8 are directed to inventions which are allegedly inoperative and therefore lack utility (Office Action, page 5).

Contrary to the Examiner's assertion, the fragments contemplated by claims 7 and 8 are indeed operative, for example, for use as inhibitors of activation of cAMP and mitogen responsive genes. Indeed the specification explicitly sets forth this activity of the claimed fragments:

> Alternative compounds which are capable of inhibiting activation of cAMP and mitogen responsive genes include polypeptide fragments comprising amino acid residues from about 461 up to 661 of the protein set forth in SEQ ID NO:2. Polypeptide fragments . . . having a mutation at residue 600 (Arg-600), set forth in SEQ ID NO:2, are preferred, while KIX polypeptide fragments substituting Gln for Arg-600 are presently most preferred.

See page 17, lines 5-14, of Applicants' specification (emphasis added). Applicants respectfully submit that these fragments are therefore, operative and that their use in the inhibition of transcription is a credible and substantial utility. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

III. 35 U.S.C. § 112, 2nd paragraph

A. Claims 1-8

These claims stand rejected under 35 U.S.C. § 112, 2nd paragraph on the basis of an alleged inconsistency between the teachings of the art and the sequence presented in SEQ ID NO:2 (Office Action, page 6). This rejection has been rendered moot by the replacement Sequence Listing transferred from parent U.S. Patent Application Serial Number 08/961,739.

B. Claims 1, 2, and 6-8.

The rejection of these claims under 35 U.S.C. § 112, 2nd paragraph on the basis that the phrase "wherein said fragment includes all or a portion of CBP which binds CREB" is allegedly unclear (Office Action, page 6) is respectfully traversed.

Applicants respectfully submit that the claims are clear as written. However, in order to advance prosecution, Applicants have amended claims 1, 6, 7, and 8 to define Applicants' invention with greater particularity. Claims 7 and 8, as amended herein, no longer depend from claim 1. Claims 1 and 6, as amended, define fragments embraced by the present claims as

"comprising residues 634-648 of SEQ ID NO:2" and further requiring that the fragment "binds to CREB." It is respectfully submitted that the claims, as amended, fully satisfy the requirements of 35 U.S.C. § 112, 2nd paragraph. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

C. Claim 6

The rejection of this claim under 35 U.S.C. § 112, 2nd paragraph on the basis that the phrase "mutant fragment" is allegedly unclear (Office Action, page 7) is respectfully traversed.

Applicants respectfully submit that the claim is clear as written. Indeed, one of skill in the art would readily understand the phrase "mutant fragment" as embracing fragments as defined by claim 1, wherein such fragments have an *alteration* in sequence (e.g., a point mutation, insertion or deletion in the nucleic acid sequence). Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

D. Claims 2, 7, and 8

The rejection of these claims as allegedly being indefinite is respectfully traversed and has been rendered moot by the amendments submitted herewith. Reconsideration and withdrawal of the this basis for rejection are therefore, respectfully requested.

IV. 35 U.S.C. § 112, 1st paragraph (Written Description)

The rejection of claims 1, 2, and 5-8 under 35 U.S.C. § 112, 1st paragraph as allegedly failing to comply with the written description requirement is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that "the application does not provide adequate written description support for any CBP protein, or for any fragment thereof that is capable of binding to CREB" (Office Action, page 9).

Specifically, Applicants disagree with the Examiner's characterization of the claims as embracing "any CBP protein" or "any fragment thereof." Contrary to the Examiner's characterization, the claims are directed to nucleic acids encoding defined polypeptide fragments, that is, polypeptide fragments with defined structural and defined functional properties.

For example, claim 1 is directed specifically to "isolated nucleic acid comprising a sequence encoding a fragment of CREB binding protein (CBP), wherein said fragment includes all or a portion of CBP which binds to CREB, and wherein said fragment comprises residues 634-648 of SEQ ID NO:2." Thus, Applicants have provided structural properties of the claimed fragments through disclosure of an exemplary sequence of CBP in SEQ ID NO:2 as well as a requirement that a fragment comprise residues 634-648.

Further, claim 1 contains a functional requirement, namely, that the encoded fragment bind CREB. Guidance is provided in the specification concerning the region of CBP which binds CREB. Indeed the Examiner acknowledges that "the application discloses a minimum region required for CREB binding as comprising residues 461-661" (Office Action, page 10). Moreover, the specification describes studies using antiserum developed against residues 634-648 of mouse CBP in which it was determined that the binding of antibody to this region is critical to the ability of the antiserum to inhibit cAMP-dependent transcription. This supports the assertion that this region is involved in formation of the CBP:CREB complex.

One of skill in the art would understand that structural information provided in the specification, through the exemplary sequence of SEQ ID NO:2 and the requirement that an encoded fragment comprise residues 634-648, in conjunction with the functional requirement that it bind CREB, fully describes the claimed nucleic acids by distinguishing them from other nucleic acids encoding polypeptides which do not share these properties.

Based on the above, Applicants respectfully submit that the structural and functional description of the claimed nucleic acids fully satisfies the written description requirement. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

V. 35 U.S.C. § 112, 1st paragraph (Enablement)

The rejection of claims 1, 2, and 5-8 under 35 U.S.C. § 112, 1st paragraph as allegedly not satisfying the enablement requirement is respectfully traversed.

Applicants respectfully disagree with the Examiner's assertion that "the claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention" (Office Action, page 11). This conclusion is based on an erroneous and incomplete analysis of the Wands factors by the Examiner, as detailed below.

1) Breadth of the claims

Applicants respectfully disagree with the Examiner's assertion that "these claims read on any fragment, or mutant of CBP, wherein such fragment or mutant is able to bind to CREB" (Office Action, page 12). As stated in the previous section, these claims are directed to nucleic acids encoding defined fragments, that is, fragments with defined structural and defined functional properties. Thus, the claims are not directed to any fragment or mutant of CBP, but rather to those fragments that comprise residues 634-648 of SEQ ID NO:2 and bind to CREB.

2) The amount of direction or guidance provided by the Applicant

Applicants respectfully disagree with the Examiner's assertion that "there is no identification of specific regions that are required for the protein's CREB-binding activities" (Office Action, page 12). Contrary to the Examiner's assertion, the specification does provide guidance as to the regions involved in binding CREB. For example,

> Within CBP, a CREB binding domain has been identified, referred to aas KIX which specifically interacts with the phosphorylated KJD domain of CREB,

specification at p. 6, lines 6-9; and

> Phosphorylated Ser133 [of CREB] coordinates with a single arginine residue (Arg-600),

specification at p. 6, lines 11-12.

Further, there are disclosed methods of identifying compounds with the binding or activating properties of CBP. See, for example, page 19, lines 1-16.

3) Predictability of the art

It is respectfully submitted that the artisan would be able to reasonably predict where mutations may be made and their effect on CREB binding, based on the teachings of the art and the teachings of the specification. The Examiner has cited a reference (Bowie et al.) in efforts to support the assertion that "the arts of protein mutation and the determination of the effects of modifications to proteins are largely unpredictable" (Office Action, page 13). The Bowie reference is unable to support the Examiner's position, and indeed supports Applicants' position. Specifically, see page 1306, right column, 2nd paragraph of the Bowie reference, where it states that "studies in which these methods were used have revealed that proteins are surprisingly tolerant of amino acid substitutions." Indeed, one of skill in the art would recognize that one could make mutations within the protein without affecting the protein's function. Moreover, the specification provides guidance as to regions or residues (e.g., Arg600) that are important in binding of CREB. Based on the teachings of the art and the teachings of the specification, one of skill in the art would be able to make reasonable predictions regarding where mutations may be made to CBP.

4) State of the prior art

Applicants respectfully submit that the state of the relevant art is quite advanced. CREB and CREB binding protein are well-known in the art. For example, an on-line search of the PubMed database at NCBI using the search term "CREB" in the title yielded 1046 articles. Similarly, a search using the term "CREB binding protein" in the title yielded 172 articles. These search results support the assertion that the field is quite advanced.

5) Nature of the invention

The invention is drawn to nucleic acids encoding fragments of CBP.

6) Level of skill in the art

The relative level of skill in the relevant art is quite high.

7) Existence of working examples

The specification provides an exemplary sequence of CBP in SEQ ID NO:2. Further, other homologous sequences can readily be found in public databases. Moreover, the specification provides examples of regions and residues of CBP that are involved in binding of CREB. Therefore, based on the examples provided in the specification and the ample information readily available to the skilled artisan, one of skill in the art is enabled to make or use the claimed invention.

8) The quantity of experimentation need to make and/or use the invention

Based on the teachings of the art, the high level of skill of the artisan, the examples and guidance of the specification the quantity of experimentation required would not be considered undue.

In summary, Applicants respectfully submit that the Examiner has mischaracterized or not properly considered each of the Wands factors in his analysis. Applicants further submit that

when all of these factors are taken into consideration, the specification provides more than adequate enablement for the claimed inventions.

VI. 35 U.S.C. § 102(a)

The rejection of claims 1 and 6 under 35 U.S.C. § 102(a) as allegedly being anticipated by Chrivia et al. (Nature 365:856-9, 1993) is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that "because the reference teaches a fusion protein [of fragments of CBP] it also teaches a 'mutant fragment'" (Office Action, page 14).

Applicants invention as defined, for example, by claim 1, distinguishes over Chrivia by requiring nucleic acids which encode a "fragment of CREB binding protein (CBP), wherein said fragment includes all or a portion of CBP which binds to CREB, and wherein said fragment comprises residues 634-648 of SEQ ID NO:2". Nucleic acids comprising such a fragment are not taught by the reference. Therefore, the reference does not anticipate the present claims. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

VII. 35 U.S.C. § 102(b)

The rejection of claims 7 and 8 under 35 U.S.C. § 102(b) as allegedly being anticipated by Parker et al. (Mol Cell Biol 16(2):694-703, 1996) is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that "the reference therefore implicitly teaches the making of a nucleic acid according to the identified claims" (Office Action, page 15).

Applicants' invention as defined, for example, by claim 7 distinguishes over Parker by requiring nucleic acids "encoding a fragment of CREB binding protein (CBP),wherein said fragment comprises residues 461-661 of SEQ ID NO:2 and wherein the residue at position 600 of SEQ ID NO:2 is an amino acid other than arginine." Nucleic acids comprising such a fragment are not taught by the reference. Therefore, the reference does not anticipate the present claims. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

VIII. 35 U.S.C. § 103

The rejection of claims 2-5 and 7 under 35 U.S.C. §102(a) as allegedly being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as allegedly being obvious over Chrivia is respectfully traversed (Office Action, page 15).

With regard to claims 2-4 (claim 5 having been canceled herein), Applicants respectfully disagree with the Examiner's assertion that these claims are anticipated (Office Action, page 15). Claims 2-4, which depend from claim 1, define nucleic acids which encode a "fragment of CREB binding protein (CBP), wherein said fragment includes all or a portion of CBP which binds to CREB, and wherein said fragment comprises residues 634-648 of SEQ ID NO:2." Nucleic acids comprising such a fragment are not taught by the reference therefore, the reference does not anticipate the present claims. Moreover, there is no suggestion or motivation to select nucleic acids comprising this fragment. Thus, the burden of establishing prima facie obviousness has not been met. Accordingly, Applicants respectfully request reconsideration and withdrawal of these rejections.

With regard to claim 7, Applicants respectfully disagree with the Examiner's assertion that this claim is anticipated. As amended herein, claim 7 requires nucleic acids "encoding a fragment of CREB binding protein (CBP),wherein said fragment comprises residues 461-661 of SEQ ID NO:2 and wherein the residue at position 600 of SEQ ID NO:2 is an amino acid other than arginine." These requirements distinguish the present claims over the reference because nucleic acids encoding such a fragment are not taught by the reference. Therefore, the reference does not anticipate the claimed nucleic acids. Moreover, there is no suggestion or motivation to select such a nucleic acid. Thus, the Examiner has not met the burden of establishing a case of prima facie obviousness. Accordingly, Applicants respectfully request reconsideration and withdrawal these rejections.

CONCLUSION

In view of the above amendments and remarks, the present application is respectfully submitted to be in condition for allowance. Accordingly, reconsideration and favorable action with respect to the pending claims are respectfully requested. In the event any issues remain to be resolved in view of this communication, the Examiner is invited to contact the undersigned at the number given below so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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